Pulmonary hypertension and Angiostrongylus vasorum

Glaus, Tony M

Pulmonary hypertension and *Angiostrongylus vasorum*

Tony Glaus, Vetsuisse Faculty University of Zurich, CH-8057 Zurich

Introduction

Pulmonary hypertension (PH) is defined as elevated pulmonary artery pressure (PAP) secondary to various pathophysiologies causing cor pulmonale and eventually right sided heart failure. The WHO classification of PH is based on similarities in pathophysiologic mechanisms (table).

Angiostrongylus (A.) vasorum is an important cause of PH in dogs in endemic areas and a most fascinating disease with many open questions despite quite intensive research in the past decade. The goal of this presentation is to put *A. vasorum* into the context of PH, to discuss the pathogenesis of the PH caused by it respectively to discuss mechanisms that may temper its development, to describe possible courses of disease in dogs with *A. vasorum* associated PH, and to suggest the therapeutic approach in critically diseased dogs.

Table: Classification of pulmonary hypertension*

Group 1. Pulmonary arterial hypertension (PAH)
Idiopathic (formerly primary PH, PPH)
Associated with congenital systemic-to-pulmonic shunts
Persistent pulmonary hypertension of the newborn
Associated with drugs, toxins, inflammatory conditions
Group 2. Pulmonary hypertension associated with left heart disease
Left ventricular or atrial disease
Left-sided valvular disease
Group 3. Pulmonary hypertension associated with respiratory disease and/or hypoxemia
Interstitial lung disease, e.g. pulmonary fibrosis
Chronic upper airway obstruction
Chronic exposure to high altitude
Group 4. Pulmonary hypertension due to thromboembolic disease
Primary cardio-vascular lesion, e.g. *D. immitis, A. vasorum*
Medical condition predisposing to pulmonary thromboembolism
Group 5. Miscellaneous
e.g. neoplasia compressing pulmonary arteries

* WHO classification, Chin and Rubin, 2008, modified and adapted for dog

Angiostrongylus vasorum

A. vasorum is a ubiquitous metastrongylid heartworm of dogs and related canids. It has an indirect life cycle with gastropods (slugs and snails) acting as intermediate hosts. The

up to 25 mm long adult worms reside in pulmonary arteries and the right ventricle. After a prepatent period of 40-60 days eggs are shed in terminal pulmonary arteries. At the same time the infection becomes patent, intense immunological reactions against eggs and larvae cause severe inflammation in pulmonary vessels (i.e. vasculitis) and parenchyma (i.e. pneumonia), with hemorrhage, arterial thrombosis, periarteritis, and coalescing granulomata. These pathological changes result in various degrees of radiographic changes.

Clinically, cough and dyspnea are the most common abnormalities, however, in some dogs respiratory signs may be completely absent but signs of various other organ systems dominate. These may include central nervous system signs, ophthalmic inflammation and spontaneous bleeding due to immune-mediated thrombocytopenia or disseminated intravascular coagulation. Also, spontaneous or surgery associated bleeding may occur without any measurable abnormality in platelet number, platelet function (buccal mucosal bleeding time) or coagulation factors (PT, PTT, TT). Pulmonary vascular inflammation and pulmonary thrombosis and / or embolism (PTE) are important mechanisms of PH, and several recent reports have documented severe PH secondary to the infection with *A. vasorum*.

Parameters that may be important to cause PH

Despite the pathophysiological expectation that *A. vasorum* should induce PH in cases infected with a high parasitic load respectively in cases with severe pulmonary lesions e.g. based on radiographs, the occurrence of PH in *A. vasorum* is quite unpredictable. Parasitic load seems a logical parameter determining development of PH. However, in experimental infection, parasitic load did not make an appreciable difference; specifically, infection with 50 larvae caused pleural effusion and quite severe pulmonary lesion radiographically as well as histopathologically, including wide spread thrombosis, but no PH; infection with 500 larvae still did not cause PH. Chronicity may play a role; however, arguments against simple chronicity again arise from experimental infection, where spontaneous recovery is detectable around 10 weeks after one single infection. Rather, repetitive infection with repetitive immunological stimulation may be an important factor. An argument in natural infection clearly against chronicity and somewhat against repetitive infection is the observation that most clinical cases of severe PH seem to occur in quite young dog, often less than 6 months of age, even

though it may occur at any age. If severe PH is found in a four-month old dog, this dog did not have much time for repetitive infection as the prepatent is close to 2 months.

Mechanism of PH in *A. vasorum*

In cases with PH, the histopathological findings indicate several mechanisms that may cause the PH, i.e. extensive pneumonia with expected hypoxia-induced PH (group 3 PH), pulmonary fibrosis (group 3), pulmonary artery thrombosis (group 4), and also pulmonary artery remodelling like in PAH (group 1).

The course of the disease in dogs with severe PH may also be quite variable. Some dogs make a miraculous recovery within a few days without any detectable PH within 1-2 weeks. In such cases, pulmonary thrombosis may be the most important cause of PH, as it would not be expected that remodeled arteries reverse-remodel so quickly.

Some dogs die within hours of initiation of therapy; as in some of such dogs pulmonary parenchymal lesions radiographically are remarkably less pronounced than in less sick dogs, again pulmonary thrombosis, i.e predominantly vascular lesions (as opposed to parenchymal lesions with alveolar hypoxia), seems the most plausible important pathomechanism of PH. The cause of death in these dogs may not only be related to the PTE, but also to therapy.

Some dogs show an initial recovery over several days or even weeks only to thereafter again develop PH, at a time where the parasites are expected to be eliminated and thus vasculitis and associated PTE should not any more be present. Interstitial lung disease with or without fibrosis would seem a logical explanation for such cases, however, this cannot necessarily be found on histopathology. Finally, severe PH may be found in dogs that show radiographic abnormalities suspicious of *A. vasorum* where histopathology fails to find an explanation for PH.

Echocardiographic findings in experimentally and naturally infected dogs

Experimental infection of dogs with *A. vasorum* allowed studying PTE including various echocardiographic and laboratory parameters. Marked pulmonary (vascular) abnormalities, including hemorrhage and thrombosis, paralleled by moderate hypoxemia with PO_2 around 73 mmHg were not sufficient to cause relevant PH nor 2D, M-Mode or Doppler echocardiographic changes.

In a second study the focus was put on newer echocardiographic modalities, i.e. Tissue Doppler Imaging (TDI) and contrast echo. A specific goal was to document arterio-

venous shunting during experimental infection and during therapy. It was further hypothesized that PH may develop right at the time of treatment, when many worms die. In this study, six healthy Beagles were infected with 200 L_3 larvae. TDI (pulsed wave, RV longitudinal myocardial velocity basal segment), contrast echo with agitated saline and pulmonary transit time with SonoVue^R, as well as invasive PAP measurement were performed pre infection (T0), once 7 to 12 weeks post infection (T1) and once during the first five days after parasiticide therapy (T2).

In the TDI variables analyzed there was a decrease in peak myocardial velocity in systole (S_{TDI}) and an increase in time to peak systolic contraction (T_{peak}) with a median S_{TDI} of 0.130 m/s (0.123-0.194), 0.128 m/s (0.087-0.173) and 0.117 m/s (0.083-0.152), and a median T_{peak} of 0.097 ms (0.074-0.149), 0.109 ms (0.102-0.196) and 0.149 ms (0.104-0.234) at T0, T1, and T2, respectively. The E/A_{TDI} ratio decreased from T0 1.13 (0.94-1.55) to T2 0.91 (0.54-1.38). At T0 all dogs showed negative, and at T1 and T2 5 of 6 dogs showed positive contrast studies for shunts. Median pulmonary transit time was 4 beats respectively 2.3 seconds at T0 and no change was observed at T1 and T2. Invasively measured PAP slightly increased over time with median sPAP of 24, 25 and 29 mmHg and dPAP of 10, 11 and 18 mmHg, respectively. Two dogs showed mild PH at T2 (sPAP 33 and 30, and dPAP 20 and 25 mmHg); both had $E/A_{TDI} <1$.

In conclusion, in dogs with marked pulmonary vascular disease and mild increase in PAP, effects on RV function were detectable using TDI but not conventional echo.

In face of severe pulmonary disease the majority of dogs opened intrapulmonary arterio-venous shunts in the absence of relevant PH. Parasiticidal therapy did cause an increase in PAP, but not to a clinically relevant degree.

Echocardiography in naturally infected dogs reveals similar changes, e.g. diastolic TDI abnormalities in cases without PH. Most interestingly, some dogs with marked radiographic abnormalities but no or mild-moderate PH show arterio-venous shunting but some dogs with most severe PH do not. This may, indeed, support the hypothesis that the opening of shunts is not just a consequence of pulmonary vascular disease or PH, but rather the ability to open such shunts may temper the development of PH. At any rate, not in all dogs with pulmonary vascular disease, e.g. caused by *A. vasorum*, the opening of shunts can be demonstrated. As a matter of fact, this has been found already many years ago.

Therapeutic approach in dogs with severe pneumonia and / or severe PH

In view of many similarities between *Dirofilaria (D.) immitis* and *A. vasorum* regarding PTE and cor pulmonale and in view of the many decades of experience in the treatment of *D. immits*, it is reasonable to extrapolate this knowledge to the treatment of complicated cases of *A. vasorum*.

There is no safe test to predict the degree of complications, but there is one simple factor that can be influenced to decrease the degree of complications, i.e. exercise restriction. The logic behind it is the following: more activity → more blood flow in peripheral vessels that are damaged by larvae, worms and associated inflammation → additional lesions like vessel rupture → additional inflammation and fibrosis → additional PH.

Specific recommendations in dogs with severe clinical disease and PH thus are:

- Oxygen cage or nasal oxygen
- Complete exercise restriction
- Slow adulticide kill using fenbendazol, 50 mg/kg q24h p.o. for 3-5 days, then a few days pause and again fenbendazol
- Prednisolone, 0.5 mg/kg q12h for 1 week, then q24h for 1 week, then q24h for 1 week.
- Pimobendan, 0.2-0-6 mg/kg div. q12h, initially i.v.
- Viagra, 2 mg/kg q8h p.o.
- In view of risk of ARDS: infusion with well-adjusted fluid balance, respectively rather negative balance, i.e. around 2 ml/kg/h.
- Sedation if very excited, butorphanol CRI, 0.1-0.2 mg/kg/h
- Consider theophyllin
- Clopidogrel
- Monitor: heart rate, respiratory rate, PH with echo

Decision about placing the dog on a ventilator:

- Clinical state (inacceptable dyspnea, weakness)
- Blood gas analysis $PCO_2 \geq 50$ mmHg

References

American Heartworm Society. http://www.heartwormsociety.org/veterinary-resources/canine-guidelines.html

Boag AK, Lamb CR, Chapman PS, Boswood A. Radiographic findings in 16 dogs infected with *Angiostrongylus vasorum*. Veterinary Record 2004; 154: 426-430.

Dennler M, Makara M, Kranjc A, Schnyder M, Ossent P, Deplazes P, Ohlerth S, Glaus TM. Thoracic computed tomography findings in dogs experimentally infected with *Angiostrongylus vasorum*. Veterinary Radiology and Ultrasound 2011; 52: 289-294.

Estèves I, Tessier D, Dandrieux J, Polack B, Carlos C, Boulanger V, Muller C, Pouchelon JL, Chetboul V. Reversible pulmonary hypertension in a dog presenting simultaneously with an atrial septal defect and angiostrongylosis. Journal of Small Animal Practice 2004; 45: 206-9.

Glaus T, Schnyder M, Dennler M, Tschuor F, Wenger M, Sieber-Ruckstuhl N. Natural infection with Angiostrongylus vasorum: characterisation of 3 dogs with pulmonary hypertension. Schweiz Arch Tierheilkd. 2010 Jul;152(7):331-8.

Kranjc A, Schnyder M, Dennler M, Fahrion A, Makara M, Ossent P, Morgan J, Deplazes P, Glaus TM. Pulmonary artery thrombosis in experimental *Angiostrongylus vasorum* infection does not result in pulmonary hypertension and echocardiographic right ventricular changes. Journal of Veterinary Internal Medicine 2010; 24: 855-62.

Matos JM, Schnyder M, Bektas R, Makara M, Kutter A, Jenni S, Deplazes P, Glaus T. Recruitment of arteriovenous pulmonary shunts may attenuate the development of pulmonary hypertension in dogs experimentally infected with Angiostrongylus vasorum. J Vet Cardiol. 2012;14(2):313-22.

Rahn H, Stroud RC, Tobin CE. Visualization of Arterio-Venous Shunts by Cinefluorography in the Lungs of Normal Dogs. Proc Soc Exp Biol Med 1952;80(2):239-241.

Schnyder M, Fahrion A, Riond B, Ossent P, Webster P, Kranjc A, Glaus T, Deplazes P. Haematological, clinical and pathological findings in dogs experimentally infected with the heart and lung nematode *Angiostrongylus vasorum*. Parasitology Research 2010; 107: 1471-80.